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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/696,530	10/24/2000	Lars Wahlberg	19313-004 (NS-4)	4889

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	11

DATE MAILED: 05/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/696,530	WAHLBERG ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 42-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 42-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *15 April 2003* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The Amendment filed 15 April 2003 (Paper No. 10) has been entered in full. Claims 1-23 and 42-56 are currently pending and are under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

3. The objection to the Oath/Declaration as set forth at pp. 3 ¶5 of the previous Office Action (Paper No. 9, 15 January 2003) is *withdrawn* in view of Applicant's replacement Oath/Declaration (Paper No. 10, 15 April 2003).

4. The objection to the specification as set forth at pp. 3-4 ¶7 of the previous Office Action (Paper No. 9, 15 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 15 April 2003).

5. The objection to claim **9** as set forth at pp. 4 ¶8 of the previous Office Action (Paper No. 9, 15 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 15 April 2003).

6. The rejection of claims **2, 4, 7, 44, 46, 48, 50, 51, 53,** and **55** under 35 USC §112 ¶2 as set forth at pp. 6 ¶15 of the previous Office Action (Paper No. 9, 15 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 15 April 2003).

7. The rejection of claims **18** and **21** under 35 USC §112 ¶2 as set forth at pp. 7 ¶16 of the previous Office Action (Paper No. 9, 15 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 15 April 2003).

8. The rejection of claims **1-23** and **43-56** under 35 USC §112 ¶2 as set forth at pp. 7 ¶17 of the previous Office Action (Paper No. 9, 15 January 2003) is *withdrawn* in view of Applicant's arguments (Paper No. 10, 15 April 2003).

9. The rejection of claims **43-49** under 35 USC §112 ¶1 as set forth at pp. 4-6 ¶9-14 of the previous Office Action (Paper No. 9, 15 January 2003) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 15 April 2003).

10. The rejection of claims **1-21** and **43-56** under 35 USC §102(b) as set forth at pp. 7-10 ¶18 of the previous Office Action (Paper No. 9, 15 January 2003) is *withdrawn* in view of Applicant's arguments (Paper No. 10, 15 April 2003).

Information Disclosure Statement

11. The information disclosure statement filed 24 August 2001 (Paper No. 5) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Oath/Declaration

12. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Kenneth Campbell did not sign the newly submitted Oath/Declaration.

Drawings

13. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: Figure 5 contains two components "A" and "B", these must be described in the specification (pp. 6). A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Maintained Rejections/Objections

14. Claims **1-21** and **50-56** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an isolated culture of neuronal cells wherein the proliferation-inducing growth factor is epidermal growth factor (EGF), wherein the neuronal cells are GFAP$^+$ and nestin$^+$, and further, wherein the neuronal cells are immunoreactive with striatal neuronal markers wherein said striatal neuronal markers are DLX1 and/or MEIS2 but said neuronal cells are NOT immunoreactive with cortical neuronal markers wherein said cortical neuronal marker is PAX6*, does not reasonably provide enablement for *any other*

proliferation-inducing growth factor or other neuronal cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims for the reasons as set forth in at pp. 3-6 ¶8-14 of the previous Office Action (Paper No. 9, 15 January 2003).

15. The Applicant traverses the 35 U.S.C. §112 ¶1 of claims **1-21** and **50-56** as set forth in at pp. 4-6 ¶9-14 of the previous Office Action (Paper No. 9, 15 January 2003) on the grounds that: **(a)** the proliferation–inducing factor is not necessarily the inventive concept on which the claims are based, **(b)** the elucidation of the specific biological activities affected by proliferation-inducing factors are unnecessary to practice the invention, and **(c)** the screening and experimentation necessary to find a growth factor that is applicable is not burdensome. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

16. The Examiner maintains the rejection under 35 U.S.C. §112 ¶1 of claims **1-21** and **50-56**.

17. In regards to "**(a)**", while the Examiner accepts that the Applicant does not consider the particular proliferation-inducing factor to be an inventive concept, it is crucial for the successful practice of the claimed invention. However, Kalyani *et al.* (1 October 1998) "Spinal Cord Neuronal Precursors Generate Multiple Neuronal Phenotypes in Culture." The Journal of Neuroscience **18**(19): 7856-7868 teaches the neuronal restricted precursor (NRP) cultures are notoriously heterogeneous and respond to a variety of extracellular signals. Kalyani *et al.* teaches that cloned cultures taken from the developing mammalian CNS (such as the cells in the claimed invention) vary in their responsiveness to neurotransmitters (pp. 7856-7866). Kalyani *et al.* also teaches the resultant reaction to a particular proliferation-inducing factor will vary depending on

the relative purity (in the sense of homogeneity of a culture) and the stage of development (pp. 7866). Even cells taken from an anatomically defined area respond differently to proliferation-inducing factors (Figure 6). Therefore a degree of uncertainty and unpredictability is present in practicing the invention.

18. Concerning **"(b)"**, the Examiner accepts that the specific biological actions of a particular proliferation-inducing agent need not been known to practice the invention. However, as presented above, the results of the use of a particular proliferation-inducing factor cannot be successfully predicted and requires extensive experimentation and characterization to use.

19. On **"(c)"**, contrary to the Applicant's assertion US 6040180 Johe (21 March 2000) reviews several papers concerning the use of proliferation-inducing factors to stimulate cell differentiation in multipotent and stem cells derived from the mammalian CNS (Col. 1-7). Noting that the use of the same growth factor (FGF or EGF) can yield different results in differentiation, cell survival, and in aggregated versus adherent cultures, US 6040180 concludes:

> "Results such as these [Col. 1-7] illustrate that identifying CNS stem cells, defining conditions that stably maintain CNS stem cell properties for long-term, and controlling their differentiation into mature cell types are neither obvious nor predictable to those skilled in this art." (Col. 7 lines 54-60)

20. Finally, regarding proliferation-inducing growth factor, the art recognizes that "factor" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. Due to the large quantity of experimentation necessary to identify all the applicable substances, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable proliferation-inducing growth factors, the absence of working examples

directed to all known proliferation-inducing growth factors, the complex nature of the invention, the unpredictability of the effects of proliferation-inducing growth factors on cells (Santa-Olalla and Covarrubias, 1995), and the breadth of the claims which fail to recite limitations for what constitutes an applicable proliferation-inducing growth factor, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

21. Therefore the rejection of claims 1-21 and 50-56 under 35 U.S.C. §112 ¶1 is hereby maintained.

New Objections

22. Claim 16 is objected to because of the following informalities: "inibitor" is misspelled. Appropriate correction is required.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claims **22, 23,** and **43-49** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method of producing a neuronal cell in vitro wherein the proliferation-inducing growth factor is EGF, wherein the neuronal cells are GFAP$^+$ and nestin$^+$, and further, wherein the neuronal cells are immunoreactive with striatal neuronal markers wherein said striatal neuronal markers are DLX1 and/or MEIS2 but said neuronal cells*

are NOT immunoreactive with cortical neuronal markers wherein said cortical neuronal marker is PAX6, does not reasonably provide enablement for *use of any other proliferation-inducing growth factor to practice the instant invention or other neuronal cells*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

24. Claims **22, 23,** and **43-49** are broadly drawn to using any one or all proliferation-inducing growth factors. The specification shows clear support for practicing the invention using EGF.

25. Daadi and Weiss (1 June 1999) "Generation of Tyrosine Hydroxylase-Producing Neurons from Precursors of the Embryonic and Adult Forebrain." The Journal of Neuroscience **19**(11): 4484-4497 teaches that growth factors including proliferation-inducing growth factors, vary in their effects on cells including astrocytes, a type of $GFAP^+$ cell (Figures 1-5). Thus a degree of unpredictability exists when using growth factors on cells, leading to a need to perform numerous experiments to practice the invention to its full scope.

26. Kalyani *et al.* (1 October 1998) "Spinal Cord Neuronal Precursors Generate Multiple Neuronal Phenotypes in Culture." The Journal of Neuroscience **18**(19): 7856-7868 teaches the neuronal restricted precursor (NRP) cultures are notoriously heterogeneous and respond to a variety of extracellular signals. Kalyani *et al.* teaches that cloned cultures taken from the developing mammalian CNS (such as the cells in the claimed invention) vary in their responsiveness to neurotransmitters (pp. 7856-7866). Kalyani *et al.* also teaches the resultant reaction to a particular proliferation-inducing factor will vary depending on the relative purity (in the sense of homogeneity of a culture) and the stage of development (pp. 7866). Even cells taken from an anatomically defined area respond differently to proliferation-inducing factors (Figure

6). Thus the skilled artisan is presented with an undue burden of experimentation to practice the invention in its full scope.

27. Also, US 6040180 Johe (21 March 2000) reviews several papers concerning the use of proliferation-inducing factors to stimulate cell differentiation in multipotent and stem cells derived from the mammalian CNS (Col. 1-7). Noting that the use of the same growth factor (FGF or EGF) can yield different results in differentiation, cell survival, and in aggregated versus adherent cultures, US 6040180 concludes:

> "Results such as these [Col. 1-7] illustrate that identifying CNS stem cells, defining conditions that stably maintain CNS stem cell properties for long-term, and controlling their differentiation into mature cell types are neither obvious nor predictable to those skilled in this art." (Col. 7 lines 54-60)

28. Finally, regarding proliferation-inducing growth factor, the art recognizes that "factor" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. Due to the large quantity of experimentation necessary to identify all the applicable substances, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable proliferation-inducing growth factors, the absence of working examples directed to all known proliferation-inducing growth factors, the complex nature of the invention, the unpredictability of the effects of proliferation-inducing growth factors on cells (Santa-Olalla and Covarrubias, 1995), and the breadth of the claims which fail to recite limitations for what constitutes an applicable proliferation-inducing growth factor, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. Claim **42** is rejected under 35 U.S.C. 102(b) as being anticipated by **US 5338839** (16 August 1994) McKay et al. US 5338839 teaches a tumor-derived cell line (U251 MG) which immunopositive for GFAP and nestin thus meeting the limitations of claim 42 (Col. 12 lines 4-68; Col. 13 lines 1-19; Table 1).

Summary

30. No claims are allowed.

31. The following art was found by the Examiner during the art search and is considered of note:

a. US 2003/0032181 A1 (Weiss and Gregg) 13 February 2003

b. US 2002/0151066 A1 (Rubenstein *et al.*) 17 October 2002

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher J. Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
May 5th, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER